~~portion of~~ a nucleic acid sequence designated in one of SEQ ID NO: 1~~, SEQ ID NO: 2, SEQ ID NO: 3,~~ SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, or an N-terminal fragment of 150 contiguous nucleotides thereof ~~SEQ ID NO: 7~~.

160. (**Twice Amended**) The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 95% identical to ~~all or a portion of~~ a nucleic acid sequence designated in one of SEQ ID NO: 1, ~~SEQ ID NO: 2 SEQ ID NO: 3,~~ SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or an N-terminal fragment of 150 contiguous nucleotides thereof ~~SEQ ID NO: 7~~.

161. (**Twice Amended**) The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 98% identical to ~~all or a portion of~~ a nucleic acid sequence designated in one of SEQ ID NO: 1, ~~SEQ ID NO: 2, SEQ ID NO: 3,~~ SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or an N-terminal fragment of 150 contiguous nucleotides thereof ~~SEQ ID NO: 7~~.

REMARKS

Claims 123-165 constitute the pending claims in the present application. Applicants cancel, without prejudice, claim 131, 145 and 150. Applicants add new claims 165 and 166. Support for the subject matter of these claims is found throughout the specification. No new matter has been added. Applicants respectfully request reconsideration in view of the following remarks. Applicants thank the Examiner and his Supervisor for courtesies extended during an interview at the United States Patent Office on October 7, 2002. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Claims 123-165 were previously rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

The claims were previously rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention. Specifically, the Office Action alleges that the specification fails to provide enablement for methods of promoting growth, differentiation, and/or survival of cells other than embryonic cells, and fails to provide enablement for the use of hedgehog polypeptides other than Sonic hedgehog. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants maintain the arguments of record that the specification explicitly contemplates that hedgehog polypeptides can be used to influence not only the behavior of embryonic cells and tissues, but also the behavior of adult cells. In further support of the methods explicitly taught by the application, Applicants have cited post-filing evidence which demonstrates that, as taught by the application as filed, hedgehog polypeptides can be used to influence the proliferation, differentiation and survival of adult cells including neuronal cells. Applicants contend that the wealth of post-filing evidence supports the enablement of the claimed subject matter. Simply put, Applicants taught that hedgehog polypeptides can be used to influence the behavior of adult cells including neuronal cells, and hedgehog polypeptides can in fact be used to influence the behavior of adult cells including neuronal cells.

Applicants have previously provided the declaration of Hank Dudek which demonstrates that Sonic hedgehog influences the fate of neuronal cells in animals following nerve crush. This evidence is only one of many examples that exist which demonstrate that hedgehog polypeptides influence both neuronal and non-neuronal adult cell fate. By way of example, Applicants provide herewith a few Exhibits which demonstrate that hedgehog polypeptides influence the proliferation, differentiation, and/or survival of adult endothelial cells, pancreatic cells, and taste buds (Pola et al., 2001; Thomas et al., 2000; Miura et al., 2001; enclosed herewith as Exhibits 1-3). Additionally, Applicants enclose herewith a copy of a declaration under 35 U.S.C. 1.132 of Lee Rubin that was submitted in copending application serial number 08/905,572 (Exhibit 4). The declaration of Lee Rubin provides evidence that both Sonic hedgehog and Indian hedgehog affect the growth and proliferation of adult cartilage explants, and furthermore that systemic administration of Sonic hedgehog induces chondrocyte proliferation in vivo. Exhibits 1-4 provide just a few non-limiting examples that illustrate the effectiveness of hedgehog polypeptides in a range of adult tissues.

Applicants also direct the Examiner's attention to the large number of examples which demonstrate that hedgehog polypeptides influence neuronal cell proliferation, differentiation,

and/or survival ("Focus on ALS", 2000; Tsuboi and Shults, enclosed herewith as Exhibits 5-6). Briefly, "Focus on ALS" is an article summarizing work presented at the Fifth Annual Diabetic Neuropathy Meeting which included a study demonstrating an improvement in both sensory and motor nerve function in diabetic mice treated for five weeks with Sonic hedgehog protein (Exhibit 5). Tsuboi and Shults provide evidence demonstrating that intrastriatal injection of Sonic hedgehog reduces behavioral deficits in rats with an injury to the nigrostriatal system caused by administration of 6-OHDA (Tsuboi and Shults, 2002, Exhibit 6). The efficacy of hedgehog polypeptides in animals treated with 6-OHDA is particularly interesting since lesions caused by 6-OHDA are considered to provide a model for Parkinson's disease.

In addition to these published studies, Applicants direct the Examiner's attention to data provided in a number of copending applications licensed or assigned to Applicants. Example 1 of United States Serial Number 09/187,387 demonstrates that administration of Sonic hedgehog reduces the deficits produced by cisplatin-induced neuropathy. Example 1 of United States Serial Number 09/418,221 demonstrates that Sonic hedgehog decreases the volume of cerebral infarct in a rat stroke model produced by occluding the middle cerebral artery. Examples 2-6 of United States Serial Number 09/325,602 demonstrate the efficacy of Sonic hedgehog in rats with a 6-OHDA induced lesions. As outlined above, such lesions are believed to provide an in vivo model of Parkinson's disease. Finally, Example 7 of United States Serial Number 09/325,602 demonstrates the efficacy of Sonic hedgehog treatment in rats following malonate-induced striatal lesions. These lesions are viewed as an in vivo model for Huntington's disease.

The Examiner has previously cited a few references in which a hedgehog polypeptide did not influence the fate of a particular neuronal cell type, and has pointed to the absence of data regarding the efficacy of non-Sonic hedgehog polypeptides in influencing adult cell types to argue that the effects of hedgehog polypeptides are extremely sensitive to the sequence of the hedgehog polypeptide. However, Applicants point out that substantial evidence exists to demonstrate that the hedgehog signaling pathway is not as sensitive to sequence variation in the hedgehog protein as the Examiner's comments suggest. Chang et al. demonstrated that mouse Sonic hedgehog can functionally substitute for either Drosophila hedgehog or quail Sonic hedgehog (Chang et al., 1994, enclosed herewith as Exhibit 7). Furthermore, much of the data cited above to demonstrate that hedgehog polypeptides can influence adult cell fate were performed using a hedgehog polypeptide derived from a species other than the species in which

the functional experiment was performed. For example, the experiments provided by Pola et al. use human Sonic hedgehog protein for in vivo experiments performed in mice, and the experiments performed by Tsuboi and Shults use human Sonic hedgehog protein for in vivo experiments performed in rats. The ability of hedgehog proteins derived from one species to function in another species demonstrates that hedgehog signaling is tolerant to some variation in the sequence of the hedgehog protein.

Applicants contend that the evidence in the field overwhelmingly supports methods of influencing the proliferation, differentiation, and survival of cells using hedgehog polypeptides. In accordance with MPEP 2164.05, when making a determination as to the enablement provided for the claimed invention, the evidence must be considered as a whole. Furthermore, "the evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05). Applicants contend that this burden has been satisfied.

Furthermore, Applicants point out that even if the claims encompass certain inoperative embodiments, that does not undermine the enablement of the operative subject matter. In accordance with MPEP 2164.08(b), "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." This standard has been upheld in the courts, and permits a claim to encompass a finite number of inoperable embodiments so long as inoperable embodiments can be determined using methodology specified in the application without undue experimentation. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976).

Given that the presently claimed methods were explicitly contemplated by the specification as filed, and given that the effective use of these methods has been borne out by the preponderance of the evidence in the field since the filing of this application, Applicants contend that the claims are enabled throughout their scope.

Nevertheless, the Examiner has previously argued that the post-filing evidence provided by Applicants is insufficient to overcome the rejection because one of skill in the art would not have been motivated to perform experimentation on adult cells based on Applicants' disclosure. Applicants wholeheartedly disagree with this argument. Firstly, the application as filed explicitly contemplates methods of using hedgehog polypeptides to influence the fate of a

number of adult cell populations, and hypothesizes that these methods may provide treatments for a number of diseases and injuries affecting adult tissues (page 63, lines 16-21). With respect to neural tissue, for example, the specification specifically contemplates the use of hedgehog polypeptides in the treatment of "(i) acute, subacute, or chronic injury to the nervous system, including traumatic injury, chemical injury, vasal injury and deficits (such as the ischemia resulting from stroke), together with infectious/inflammatory and tumor-induced injury; (ii) aging of the nervous system including Alzheimer's disease; (iii) chronic neurodegenerative diseases of the nervous system, including Parkinson's disease, Huntington's chorea, amylotrophic lateral sclerosis and the like, as well as spinocerebellar degenerations; and (iv) chronic immunological diseases of the nervous system or affecting the nervous system, including multiple sclerosis." (page 63, lines 24-31). Given the possibility that hedgehog polypeptides could be used to treat a range of diseases and injuries of adult tissue, Applicants contend that one of skill in the art would certainly have been motivated to practice the invention.

The Examiner has previously argued that the application, as filed, teaches away from the use of hedgehog polypeptides in adult tissues. However, as Applicants have previously stated, expression of hedgehog, or any extracellular signaling protein, in a tissue is not required for that tissue to be sensitive to signaling activated by that extracellular signaling molecule. It is the expression on particular cells of the receptor for that signaling molecule that is required for the tissue to be sensitive. In the case of hedgehog signaling, one of skill in the art would expect that cells which can be influenced by treatment with a hedgehog polypeptide should express the receptor patched. Applicants note that the application provided no evidence regarding expression of a hedgehog receptor that would guide one of skill in the art away from practicing the methods disclosed in the application.

Applicants additionally point out that medical science is rife with treatments that involve administering protein and non-protein drugs, which are not endogenously expressed, in order to achieve a beneficial effect. Certainly humans don't endogenously express aspirin, and yet this compound is taken daily by millions of people to treat a range of conditions. Furthermore, specific hormones are now typically prescribed to replace hormones whose levels are either reduced with age or lost due to disease or surgical intervention. Estrogen replacement therapy is used, not only for menopausal women whose estrogen levels are declining, but also for women who have undergone ova-rectomy or radical hysterectomy. Such women no longer

endogenously express estrogen, and yet the persistence of estrogen receptors allows their bodies to respond to exogenously supplied estrogen. Similarly, some men who undergo surgical castration to treat testicular cancer are given exogenous testosterone. These examples indicate that one of skill in the art would not construe the mere absence of expression of a particular protein as evidence that the protein would not be useful.

Although Applicants contend that the specification provided ample motivation to practice the invention, one of skill in the art did not have to rely on the teachings of the application alone to provide the impetus to practice the methods provided in the disclosure. Prior to the filing of this application, the idea that signaling molecules were used over and over again throughout both embryonic and adult development was appreciated. Applicants cite two reviews published prior to the filing of the present application which demonstrate that the field of cell and developmental biologists already appreciated the concept of using proteins expressed in embryonic tissues to treat conditions in adult tissues (Robinson, 1993; Reynolds and Weiss, 1993; enclosed herewith as Exhibits 8 and 9).

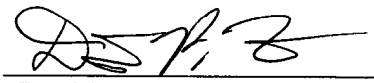
Robinson reviewed the contents of a conference on neurotrophic factors which was held in Cambridge in 1993. One topic reviewed in this article relates to work performed at Genentech on NT4/5 that demonstrated that NT4/5 plus BDNF promotes the survival of rat embryonic dopaminergic neurons in culture. Based on these results in embryonic tissue in culture, the authors hypothesized that "administration of NT4/5 or BDNF might prevent or slow the degeneration of dompaminergic neurons in Parkinson's disease." (Robinson, 1993, page 497, column 3).

Reynolds and Weiss reviewed recent developments concerning the potential therapeutic use of growth factors in treating conditions of the central nervous system. Specifically, the review focused on glial derived growth factor (GDNF) and ciliary neurotrophic factor (CNTF) "on the basis of their potential for treating human neurodegenerative diseases and their current exploitation by biotechnology or pharmaceutical companies." (Reynolds and Weiss, 1993, page 734, column 2). The hypothesis that GDNF may provide a treatment for neurodegenerative diseases came from the initial observation that GDNF enhances dopamine uptake in embryonic rat rostral mesenchaphalon culture (page 735, column 1).

These reviews indicate that, as of the time of filing, one of skill in the art appreciated that signaling molecules which are expressed and function in embryonic tissue are also used in adult

and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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